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THE ANTITHESIS OF STRUCTURE AND FUNCTION IN RENAL ACTIVITY

THE PROBLEM OF ITS CORRELATION IN THE NEPHRONS AND THE KIDNEY AND AN APPROACH TOWARDS ITS RESOLUTION BY STRUCTURAL-FUNCTIONAL EQUIVALENTS*

The Twenty-Second Middleton Goldsmith Lecture

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As an expression of the gratitude which I feel towards my fellow members of the Society for the honor of the Middleton Goldsmith Lectureship, it may be appropriate that its subject be one which so closely concerns their daily activities. For the professional life of the pathologist is little more than a series of problems in correlation which, in their practical application, usually take some turn of the time-worn question, "Has Structure determined Function in the case before me,

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and if so, in what manner?"

As I thus put the question in its classical form, two "things", that is, abstractions, concepts, postulates—call them what you will—are set in antithetical contrast with the implication that one can be "explained" in terms of the other; some sort of causal relation between the two is thereby assumed and in fact is expressed by the use of the word "determine". It is apparent at once from the logical structure of our question that we have involved ourselves not only in the most fundamental of ontological problems, the existential nature of our subjects, Structure and Function, but also in the complications of pre-Humean causality.

Now the busy pathologist need not endeavor to trace his way through the veritable epistemological morass which thus confronts him; he appreciates that it all began with Plato's curiously paradoxical suggestion that what is obviously apparent is not really real, and he recalls that the interminable disputations of the medieval Realists and Nominalists came to an uneasy equilibrium in a general acceptance of the system of Cartesian dualities. Their series is endless: Body-Soul, Matter-Mind, Mass-Energy, Structure-Function. We shall not inquire too closely into the intellectual content of these symbols, the Scholastics who were much better than we can hope to be at this sort of thing having exhausted the situation with no remarkable success; but it is disturbing to the Pathologist to be left with the implication that what he is dealing with are two things, one a more or less passive lump (Structure) that in some manner is infused with something (Function) which is more vitally "dynamic"; or as Professor Ryle describes the duality of Body-Mind, with a "clock inhabited by a ghost"[1]. Yet to such crudity of concept are we forced, if the duality is maintained, and the Pathologist is perhaps the more distressed since he is left holding the "lump" while his confrère, the Physiologist, is free to "soar on the conceptual wings" of the Dynamic.

And so we might dismiss the situation as a problem in human behaviour. Those who *like* Dualities and Antitheses, and there are many such, might be allowed to enjoy them, and those who are irked by their implications might reject them, pointing out that they arise from a certain form of our statements which, if one prefers, can be put in other terms and the dilemma so avoided.

But for the pathologist a more practical point is involved than an exercise in Linguistic Analytics; in his daily job he must accept the

duality which is passed on to him by his clinical confrères, and so he has come to make use of an intellectual gymnastic that not only solves his own dilemma, but which even at times puts him one-up in the game of the Clinico-pathological Conference. To this end, the Hegelian Dialectic, however suspect in certain politico-ideological circles, proves an effective ploy.

The *modus operandi* of this ingenious mental gambit would not concern us at this point if it had not become such a smoothly working part of our daily thinking that we are rarely aware of its operation. We do not appreciate that it is we who by *Analysis* have neatly separated the various phenomena of the disease before us into *Thesis* and *Antithesis*, assigning Structure to the pathologist and Function to the clinician. The almost schizophrenic ambivalence that thus results is clearly of our own doing and its origin is not inherent, as will become apparent later in our discussion, in "qualities" peculiar to the observational data.

But it is in the next step where the "correlation" is consummated that temptation at times arises for a bit of artful intellectual dodging; and this is not surprising, for this process of *Synthesis* of our dubious duality is at best a mysterious operation; just *how*, the skeptical Pathologist may ask, do the twain become one?

In certain situations there is at least a pragmatic answer; if we can perform the transformation on the basis of a causal connective, the result, though it might not have satisfied David Hume entirely, will be accepted as useful by the busy practitioner, whether pathologist or clinician. But in many instances this Synthesis of our structural-functional antithesis is linked by causal chains so tenuous that it is difficult to believe we have accomplished more than to restate our problem in a form which is only verbally more impressive. For example, the correlation of the structural-functional disturbances that are observed when a renal artery is obstructed by a thrombus can be accepted on a causal basis by all but the most intransigent of the modern Analytical School; but to perform the miracle of Synthesis by the suggestion that some functional disturbance, say the retention of a product usually excreted in the urine, "correlates" with a certain tubular protoplasmic disturbance, "cloudy swelling", which we have *a priori* postulated as "regressive", is not so much to stretch the "causal lines" of Russell[2, p. 453] to the point of invisibility as to twist them into the snarl of an obvious redundancy.

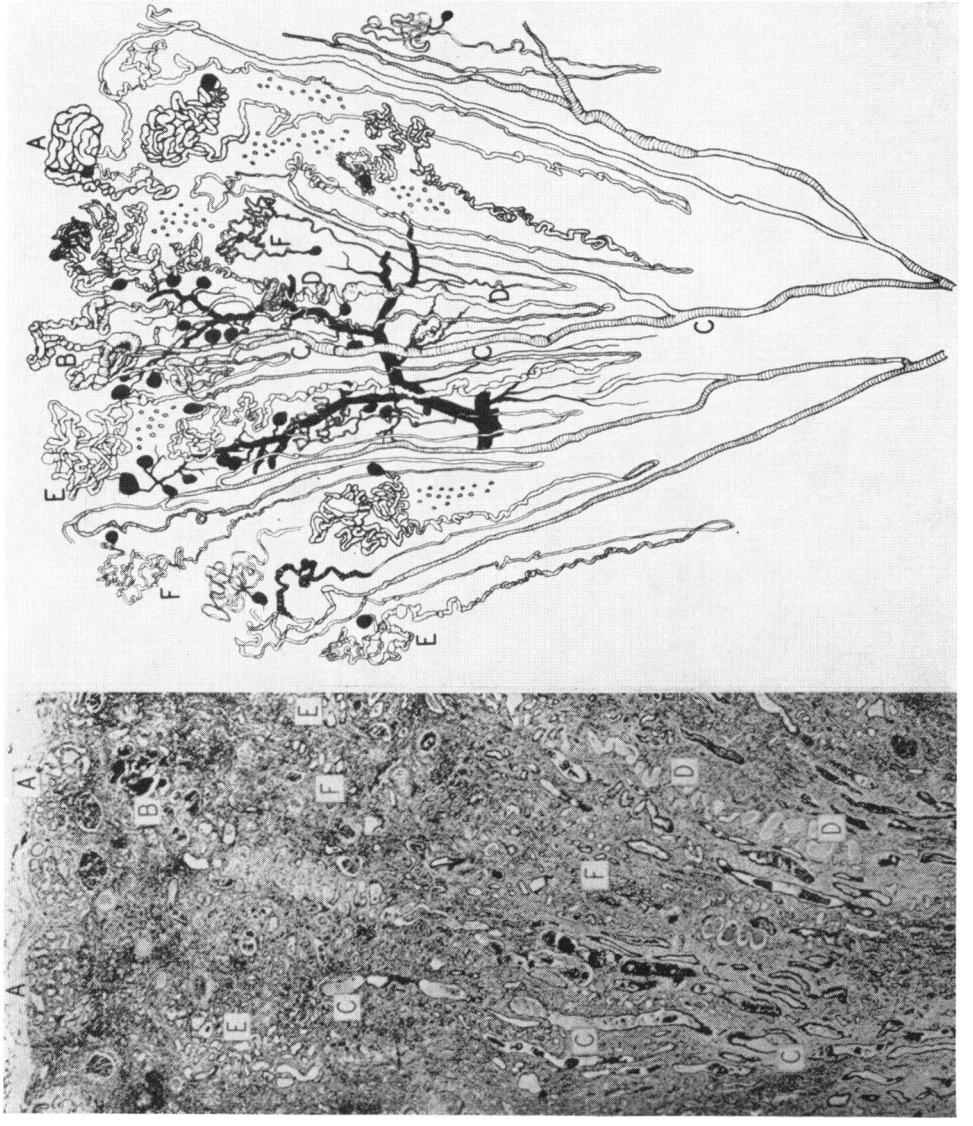

Figure 1

Granting the pragmatic value of the causally established Hegelian correlation of Structure and Function, several practical problems still remain in its application to phenomena of renal activity. The first of these is the nature or form of the data, structural and functional, on which the correlation is to be built; it is obvious if either term is wanting in validity that the operation will be spurious, and that no amount of strength on one side of the structural-functional equation can bolster the weaker member. Now the functional data of the clinician or physiologist is, in general, objective and quantitative, while the structural contribution of the pathologist is subjective and qualitative; the technician's figure of so many milligrams per cent stands, but the nature and the relative degree of tubular and glomerular involvement shifts, turns and at times even reverses itself as the protocol ascends through the staff hierarchy from Resident to Professor.

It is not clear how, in such a situation, we can do better than to settle for the best-received opinion that may be available; but these difficulties which seem inherent in the morphologist's way of looking at things are compounded by the entirely unnecessary complication that he rarely looks at and can therefore give us not even an opinion based on observation as to the state of the organs, the nephrons, the functional attributes of which constitute one-half of the correlative problem. Limiting his examination to the use of the histological section, he employs a method which indeed affords a wealth of detail concerning the nature of the processes of the renal lesion, and thereby much substance for diagnostic originality and taxonomic elaborations, but nothing in the way of information that can follow the functional changes which are occurring as glomerular filtrate passes down the tortuous conduit of the tubule to become urine. It is therefore understandable why the "Clinico-pathological Correlation", which dutifully closes the chapter on Renal Disease in the textbook, or which summarizes the autopsy protocol, so often leaves us with a bemused air of ingeniously contrived realistic unreality that might be described as worthy of Kafka.

These difficulties which stem from the disparity of the correlative data can, in part, be eliminated if the pathologist will at least *look* at the organs which are functioning. Figure 1 illustrates better than any words the difference between the two sorts of structural information which are afforded by microdissection and by the histological section.

By the former are revealed the shape of things not only in the individual nephrons, but more importantly in the now heterogeneous collocation of altered nephrons that constitute the abstraction we call an "abnormal kidney"[3]. The data are grossly oversimplified in their presentation: but may I add, since we are all so thoroughly conditioned by the subjective interpretations of the diagrams[3, p. 375] which appear in the literature of the physiological textbook and the pharmaceutical brochure, that what is shown is an assemblage of *camera lucida* tracings of the actual nephrons dissected from a specific example of renal disease. The cellular detail which would bring us closer to the boundaries where structural and functional phenomena impinge have been omitted; they have indeed in the great majority of abnormal renal situations not as yet been worked out. But the way is open for the application of all the revealing techniques of the present day, histochemical, radiographic and enzymatic procedures and electromicroscopy, if only the hands can be found to garner the harvest. Until that time comes, we can at least draw one conclusion from the oversimplified prospect that we see in my figure; and that is an appreciation of the infinite complexity of the renal lesion.

I think the clinician and also the physiologist who works with the *relative* homogeneity of the normal kidney, a situation which we shall examine later in some detail, might at least prepare himself for his attack on the problem of functional interpretation by a thoughtful moment of contemplation of Figure 1, for it shows the stark structural reality which he must face when a correlation is to be made. The present tendency is to look the other way and, since the morphologist has given him only a structural adumbration of the organ he is examining, for the functional investigator to invent a sort of meta-structure on which to base his reasoning. A "lobule" is thus described[4, p. 13] quite different from that which the morphologist finds when he takes the kidney apart, or when the "distal tubule", of which we hear so much in current literature, replaces the anatomically defined *distal convolution* along with one knows not what other well-established structural segments of the nephron. Such "structures" are clearly the result of much taking of thought and the morphologist may be gratified by the attention that is being paid to the cultivation of what he has always considered his own small garden. At times, however, he becomes uneasy lest, in some quasi-platonic sense, being led down the idealistic path of

F. H. Bradley[5], the *Appearance* he sees in his dissections may come to be considered less veridically real than the *Reality* of these ideological constructs.

Such whittling-away of the structural obstacles towards a quick and easy comprehension of renal activity reminds me that I have not mentioned one forthright resolution of the structural-functional antithesis, which, though its appeal to an audience of pathologists may be small, demands a passing note. It may be summarized as the Attitude of Transcendental Negation, for it boldly cuts the Gordian knot of our antithesis by denying that Structure has *any* existential relation to Function. Whatever the meaning of the "bizarre" configurations and patterns that the morphologist sees, they, as some idiosyncratic, perhaps aesthetic, manifestation of the Creator, may be ignored in the serious business of understanding the Kidney; for we are told: "der Fundamentalsatz nach dieser Richtung lautet: die Nieren-Funktion an sich ist in ihrer Veränderung unabhängig von der anatomischen Art der Erkrankung"[6].

Such was the prevailing climate of opinion among the clinical intelligentsia during the youth of your elder Members; against it they have fought the long, and for them, good fight along with such valiant allies, to cover a wider period, as Richard Bright and Homer Smith, on whose title pages "Morbid Anatomy" and "Structure" stand opposite and coequal with "Symptoms" and "Function". This ideological conflict is therefore worthy of a passing historical note, if not also because it may offer a psychological clue to the intransigence of an elderly Pathologist who may seem overly concerned with the King Charles head of his structural-functional antithesis.

In fact, the battle against what may fairly be considered a form of obscurantism, since it rejects one half of the evidence as irrelevant, like that for "Freedom", is never definitively won. A recent editorial[7] with de Coverley-like reasonableness seems to suggest that much may be said on both sides of the argument; that one may enjoy his structural cake but need not eat it if it appears too rich for easy digestion, or, to continue the gustatory metaphor, that the wise man will handle his Structure like strong drink, knowing when to take it and when to leave it alone. The fallacy in this seemingly temperate and certainly convenient attitude, which accepts a relation between Structure and Function until the going gets hard and the "bizarre" nephron is counted odd man out,

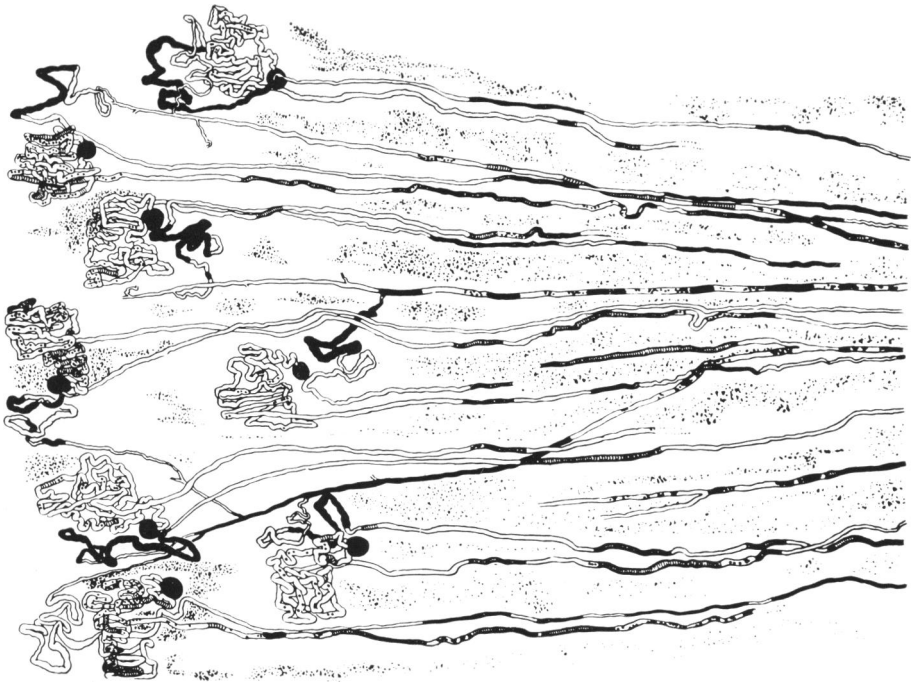

Figure 3

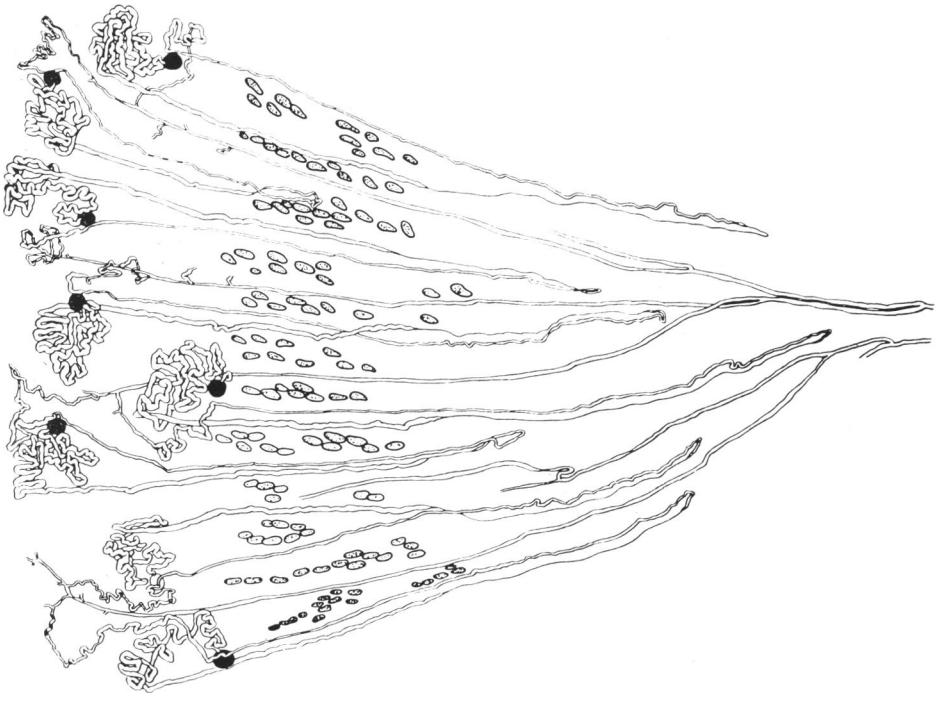

Figure 2

stems, as I shall endeavour to show, from a primary fallacy in the question it begs; that is, the assumption of the antithetical duality of Structure and Function.

Our immediate concern is not, however, with the self-searchings of the rejected Morphologist but with the meaning of structural-functional correlations to those who still believe in them; and it would seem certain that to correlate a "Structure" that has been derived hypothetically from Function, with Function as it is observed, is to indulge in a tautology which accomplishes nothing.

If the structural complexity of a chronic renal disease such as glomerulonephritis (Figure 1) seems for the present beyond our powers of exact functional interpretation, at least something can be accomplished in the much simpler situation of Acute Renal Failure, in which a kidney of normal structural configuration is damaged by a combination of ischemic and toxic insults[8]. Both the resulting functional disturbances of oliguria and diuresis can be related to the structural changes that are seen in the nephrons; the phenomena of diuresis can indeed be traced to the intracellular level, where structural alterations in the mitochondrial organelles of the tubular cells coincide with enzymatic deficiency and the failure of transport processes[9].

The renal lesion in Epidemic Hemorrhagic Fever, a special case of Acute Renal Failure[10], affords a particularly favorable example for such correlation, as here a dramatically varied clinical course proceeds, phase-like, through a diversity of functional renal disturbances which can at least tentatively be understood in terms of the concomitant changes which are seen in the nephrons. In Figures 2 and 3 are shown these structural configurations in the markedly different clinical situations of the early Hypotensive Phase and in the succeeding Phase of Oliguria. In these contrasting clinical states the relatively simple difference between the lesion of congestion and of hemorrhage in the outer *medulla* has produced contrasting changes in the nephrons that are compatible with the functional disturbances.

So far I have discussed only the practical difficulties which are inherent in the Hegelian correlation of Structure and Function as it is applied by the pathologist in his daily chore of dealing with kidneys. At the higher conceptual level more disturbing uncertainties arise when, for example, the clinician inverts the classic question, "Did Structure determine Function?", and points out that Function obviously may

determine Structure. The more thought the pathologist now gives to his answer in any given case, the less certain he becomes in which direction it should run. To return to the thrombus in the renal artery: although it would seem clear that the structural occlusion "determined" the localized ischemia, was not the origin of the structural characteristics of that thrombus, even to the configuration of its Zahn's lines, determined by the functional flow? And, entangling himself further in his philosophical analysis on a higher level of abstraction, in which he shifts his position and mixes his subjects and predicates, surely it was the absence of functional flow and the resulting anoxia rather than the structural attributes of the thrombus that produced the damage.

The usual escape from these semantic entrapments is to quote Childs' metaphor of the biological process as a river, the flow of whose waters is the dynamic flood of Functional Activity and whose banks are the static form of Morphological Structure; each, by erosion or deflection, determines the other. But this solution, it would seem to those who really dislike dualities and antitheses, is at best only a poetical way of begging the question; for, to continue Childs' analogy, it is to plunge boldly from the solid bank of Structure into the shifting Functional flood and then scramble back again to the safety of a Structural *terra firma*. The correlation thus becomes an interminable series of mental acrobatics that give much evidence of intellectual agility but little of any assured philosophical equanimity on the part of the pathologist.

Now a statement which runs in both directions, as our question seems to do, may be suspected of hiding a tautology and this suspicion leads us to look to the modern philosophers for some solution of our problem that might eliminate both the duality and its antithesis.

Professor Woodger, who devotes six chapters of his Biological Principles[11] to the resolution of various antitheses that plague the biologist, reassures us that between Structure and Function there need be none; to quote, "Far from being insoluble it is the easiest of all antitheses to overcome. A little reflexion will show that it rests simply on the separation of space and time and if this separation is not made, the antithesis between structure and function falls to the ground".[11, p. 237] From the pages which follow, it is not apparent how the biologist is to remove his problem from the realms of "space and time". Nor does the statement that "what the anatomist deals with is an *object* not an *event*" reassure him, especially as the inert concreteness of that object is em-

phasized by repeated statements that it is usually "pickled"*. In any case, we are told by another eminent philosopher that *events* have structure and therefore would seem to share the attributes of *objects*[2, p. 250].

And so the Pathologist takes his leave of the Groves of Academe, confused by resolutions of his problem that seem not only contradictory but which at best are purely verbal and undemonstrative. Everyone, as Mark Twain said of the weather, talks about the antithesis of Structure and Function, but no one *does* anything about it.

Now in one scientific area something has been done about duality and antitheses and not, to paraphrase the poets, with the "whimper" of metaphysical periphrasis but, in that "shot heard round the world", with a most demonstrative "bang". I refer to the resolution by the physicists of their fundamental duality of mass-energy by the simple statement of an equation of identity: $E = MC^2$.

To suggest that the biologists, and in the person of their not most avant-guarde examplar, the pathologist, can follow in the way of the pioneers of the present day Queen of the Sciences, may seem at first blush unlikely, but let us see how far he can go towards such a direct and forthright resolution of his duality and its antithesis.

On a former occasion I made a tentative approach to such an endeavor and in the light of its obvious failure promised to try again[12]. A very considerable amount of quantitative data, both structural and functional, is the first requisite in any such procedure, so that whatever success I may report on this second attempt is due to the aid and counsel I have received from my collaborators, Dr. Stanley Bradley and his group, who performed the functional experiments to be described, and Muriel MacDowell, who did the dissection.

Any attempt at a correlation by dimensional identity between structure and function in the area of renal activity must begin with the recognition of the fact that its solution may lie on one of a succession of observational levels[13]. From the viewpoint of renal structure we can deal with what, in the light of the revelations of electromicroscopy, has become a series of infinite regress: the kidney, the nephrons, the renal cells, the intracellular organelles such as compartments and mitochondria, and these each with their internal systems of membranes and

* This evocation of the image of the dusty corridors of the Mid-Victorian Anatomical Museum seems hardly relevant to the activity of present day morphologists, who in their daily routine follow the progress of, say, intracellular mitochondrial transformations in the living cell by means of time-lapse phase microscopy. And even when "pickled", renal biopsies taken in series during the evolution of a disease become cinematographic "frames" which denote progress in time.

"double" membranes. Membranes are not simple sheets of substance, but, as we know from Langmuir's demonstrations, spatially oriented molecules, and this structural pattern affects their qualities. Molecules, in turn, and their dynamic properties, are dependent on both their atomic content and the pattern of its configuration; so far as we can see, or indeed imagine, structural relations prevail.

From the viewpoint of renal function we may be concerned in our correlation with urine/plasma ratios and a great variety of data derived from observations which indicate the movement, i.e., the "transport" of ions or molecules from one place to another, usually across membranes. The site of these movements can be localized and their magnitude measured by a diversity of technical procedures which vary in their objectivity from the relative certainty of Richards' sampling by micropuncture to the rather lesser exactness of those recent ingenious refinements of the urologists' two-glass test which are designated as "stop-flow analyses".

Much of the difficulty, and most of the confusion, in past attempts at correlation have come, I believe, from observation on one level, or an ill-defined or even unknown level, with inference operating on another. Both the investigator of function and the morphologist are subject to this error, the latter surely with less excuse, as he should be able to see what he is doing. I must, therefore, explicitly define the observational levels with which we shall be concerned.

The renal correlation I have chosen as a test case will describe how the kidney and the nephrons handle glucose; from the structural standpoint we shall consider the spatial dimensions of two components of the *nephron*, the glomerulus, through which glucose enters the lumen of the tubule, and the proximal convolution by which it is removed from the tubule fluid. On the functional side, we shall be concerned with relations between concentrations and amounts of glucose in the blood passing to the *kidney* and those observed in the urine leaving it. No difference in observational level between kidney and nephron is here involved, for the data derived from the kidney, as will be apparent, can be reduced to the common denominator of the nephron by what has been learned through direct visual observation and quantitative measurements with the methods of micropuncture and microdissection[14]. We also know from these procedures that no other parts of the nephron are concerned in the handling of glucose.

The development of the correlation will proceed as follows: first, a general examination will be made of the situation in the normal human kidney comparing structural measurements we have recently completed with functional data derived from the previous studies of Dr. Homer Smith and his coworkers[15]. As a result of this comparison and a consideration of Dr. Smith's theoretical analysis I shall then propose certain *structural-functional equivalents*, the validity of which will be tested by their use in the quantitative description (titration) of the handling of glucose by the kidney and nephrons. Certain specific aspects of the problem which have arisen in this general survey will then be reexamined, using structural and functional measurements made on the kidney of the dog; the latter were done by Dr. Stanley Bradley's group.

THE STRUCTURAL DATA IN THE HUMAN CASE

It is commonly stated that the length of the proximal convolution in man is 15 mm., a figure based on Peter's[16] measurements of five nephrons in three individuals of unknown age and weight. Pai[17], on the other hand, measuring nine nephrons from three "young men", found a mean length of 20.1 mm. The glomerular measurements of the two investigators differ even more, being 155 μ and 300 μ respectively for average glomerular diameter. It is clear, therefore, that we start with no firm data regarding even mean values and none at all in regard to the distribution of variations in size of the renal elements.

We have measured by means of microdissection the dimensions of 104 glomeruli and their attached proximal convolutions in three young normal adults who died of acute accidents*.

First, as to the length of the proximal convolution: it is this dimension which has been mentioned most frequently as a possible determining factor in the reabsorption of sugar and has therefore been suggested as a structural correlate[15, p. 105]. It is seen in Figure 4 that, although there is some irregularity in the symmetry of the histograms of the individual cases, the mean and ranges are similar, and that consolidation of the 104 examples produces the figure of a normal frequency distribution.

But can simple length of the convolution be an adequate measure of its functional potentialities? Would not a thick, but shorter tubule contain as much or more active protoplasmic elements, such as the enzymes

* The detail of this and other technical procedures along with a fuller statement of the problems encountered and the rationale of their solution will be found in a future issue of the *Journal of Clinical Investigation* (in Press).

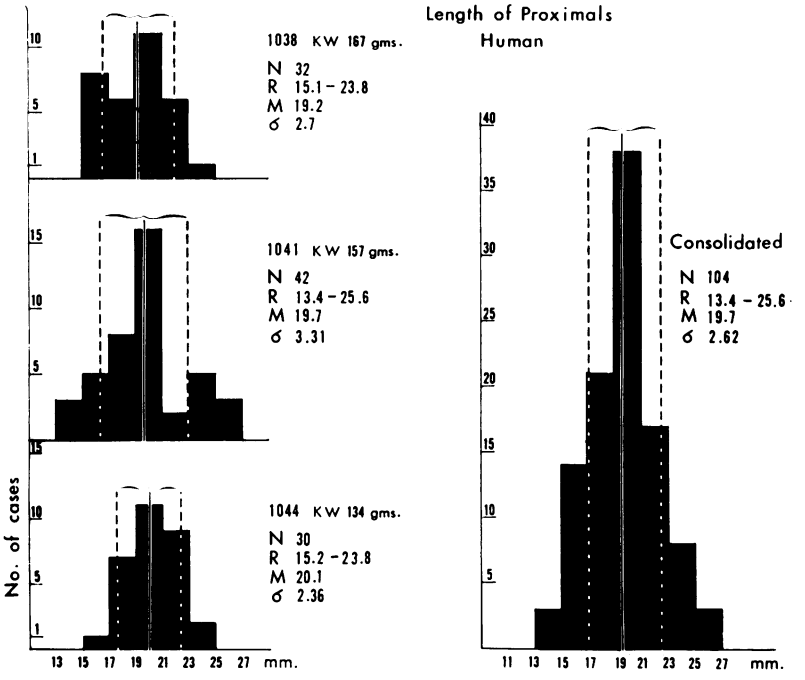

Figure 4

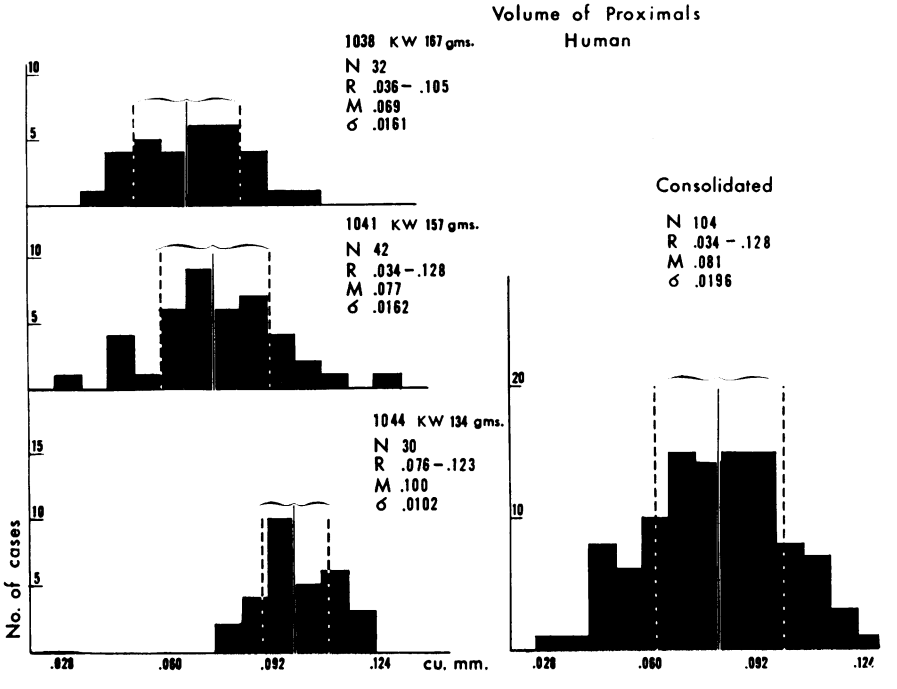

Figure 5

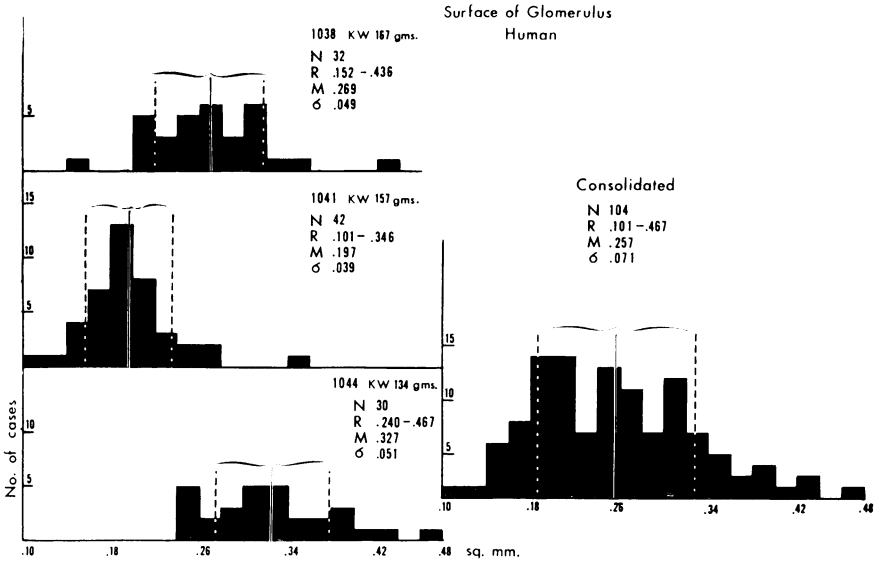

Figure 6

and substrates that are essential factors in its function? Moreover, the functional procedure with which we shall be concerned measures the degree of *saturation* of the reabsorption mechanism, and this might seem to correlate more appropriately with the mass of the tubule cells. The volumes of the same convolutions are shown in Figure 5, the average of 10 measurements of diameter in each convolution being used in the calculation. More variation in range and mean are observed between the individual cases than in the case of length of convolution, but again consolidation of the data gives a statistical distribution in the normal pattern.

In considering the dimensions of the glomerulus in the light of its function as a filter, the surface of the tuft might seem to be a factor of importance. In Figure 6 it is seen that the glomeruli attached to the regularly distributed convolutions vary considerably in this regard in the three individuals as to mean and range and that consolidation of the data produces a frequency distribution with a definite skew. On the other hand, it has been argued that the essential mechanism of filtration is determined within the tuft at the capillary surface and that this dimension, too involuted for direct measurement, would best be approximated by the volume of the mass of its blood channels[18, p. 570]. The results of calculation of the volume of the tuft made from the average of the two somewhat different glomerular diameters are seen in Figure 7

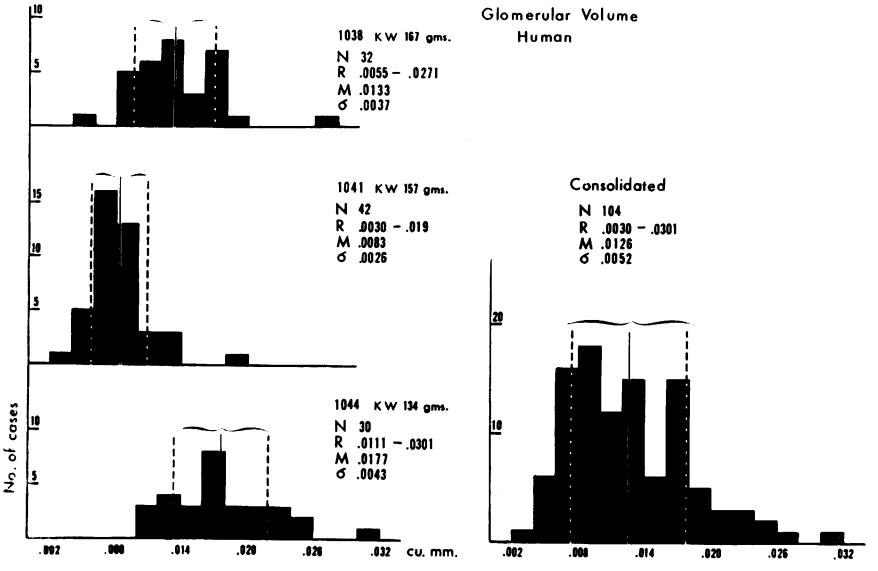

Figure 7

to give statistical patterns not unlike those observed in the comparisons of the tuft surfaces both in regard to variation in range, mean values and in distribution.

We see, therefore, that the population of nephrons in the normal human kidney shows a considerable degree of variation in structural dimensions of various sorts. We have available for correlation with function at least four different sets of these variables; surface and volume of the structures which put glucose into the nephrons, and length and volume of the elements which remove it. Since the size of the glomerulus and the proximal convolution vary in each nephron and the functional capacity of each nephron can be assumed to be the resultant of this relation, it is clear that in our use of structural dimensions for comparison with the functional data we cannot deal with the generality of mean values, but must keep intact the integrity of the organs we are examining, the nephrons, by relating each individual structural glomerular datum to its own particular tubular dimensions. In other words, our correlation must be concerned with the structural aspect of glomerulo-tubular balance in the individual *nephrons*, and only from a consideration of the totality of these individual ratios can the description of the physiological behavior of the kidney be derived.

We have already seen that the approach by inference to a decision as to which of the various dimensions of glomerulus and proximal convolution will be the most appropriate for the correlation with the functional description is uncertain in the case of both tubule and glomerulus. We therefore leave the choice of the correlates to the results of statistical analysis. The justification for this conclusion is the well-established biological principle that in a population of individuals, those who work together, grow together.

In Figure 8 the length of the proximal convolution of each nephron is plotted as abscissa against the surface of its attached glomerulus as ordinate in 104 examples from the three individuals. It is clear that there is little evidence of any structural balance between these two dimensions of glomerulus and tubule; over a range of proximal length of 13 to 24 mm., glomerular surfaces of from 0.100 to 0.460 sq. mm. are randomly scattered. Nor is the relation improved if glomerular volume is compared to tubule length as in Figure 9.

If, however, the volume of the proximal convolution is plotted against glomerular volume, a closer relation is seen (Figure 10) in that the points begin to follow the line which represents a proportional balance. When glomerular surface and proximal volume are used as the coordinates, an even closer relation is found (Figure 11). The dimensions of the smallest nephron (glomerular surface 0.100 sq. mm.—proximal volume 0.035 cu. mm.) and the third from largest (glomerular surface 0.420 sq. mm.—proximal volume 0.120 cu. mm.) both lie quite near the line of equivalent glomerulo-tubular structural balance.

It would seem, therefore, that the dimensions of glomerular surface and proximal tubule volume are the most promising structural data for correlation with the functional aspect of our problem.

Before proceeding to this correlation, we may briefly recall certain elementary features of the manner in which glucose is handled by the nephron. We know from direct observation[19] that the sugar enters the mammalian proximal convolution in the same concentration as obtains in the blood, and if this level is not greater than that which usually exists under "physiological" conditions, it has, for all practical purposes, disappeared at the mid-point of this segment of the tubule. One half of the proximal convolution is thus normally "in reserve"; this, roughly the terminal medullary portion, may therefore be considered the *structural equivalent* of what has been expressed in functional terms as

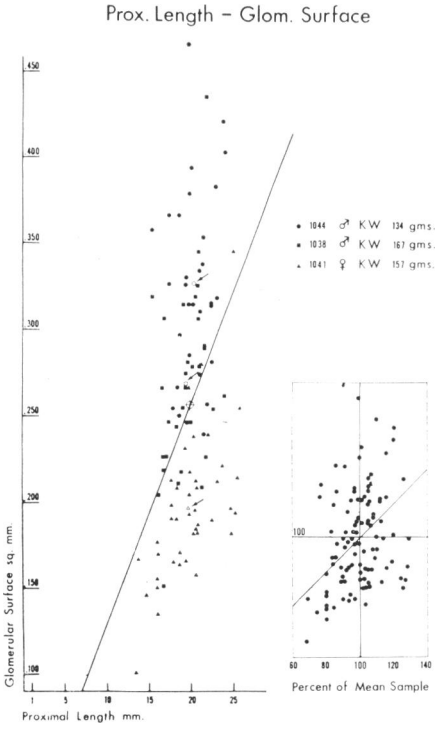

Figure 8

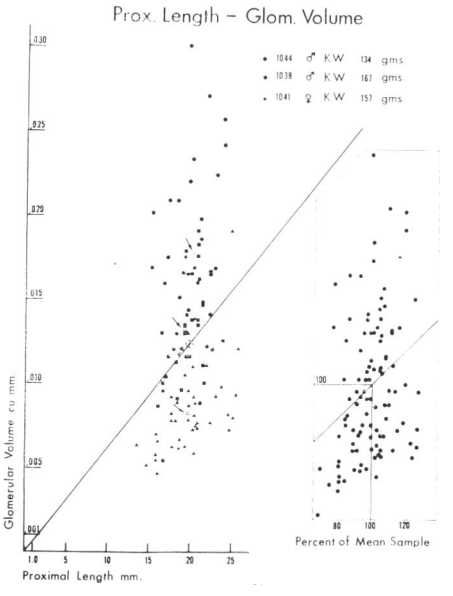

Figure 9

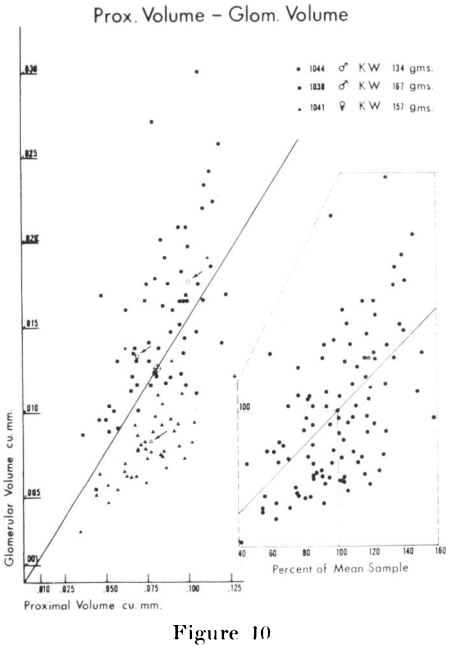

Figure 10

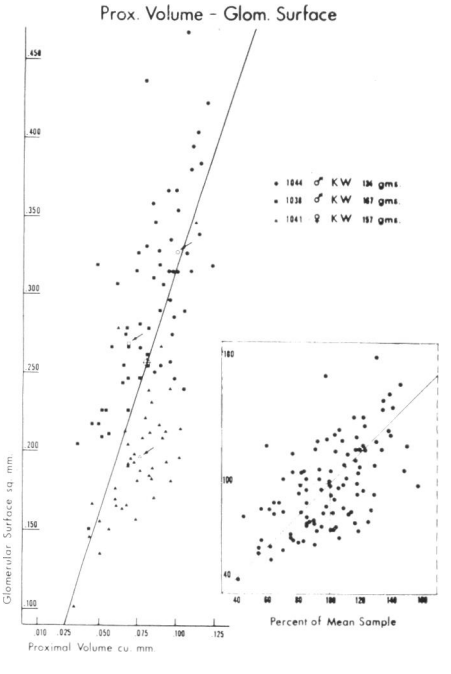

Figure 11

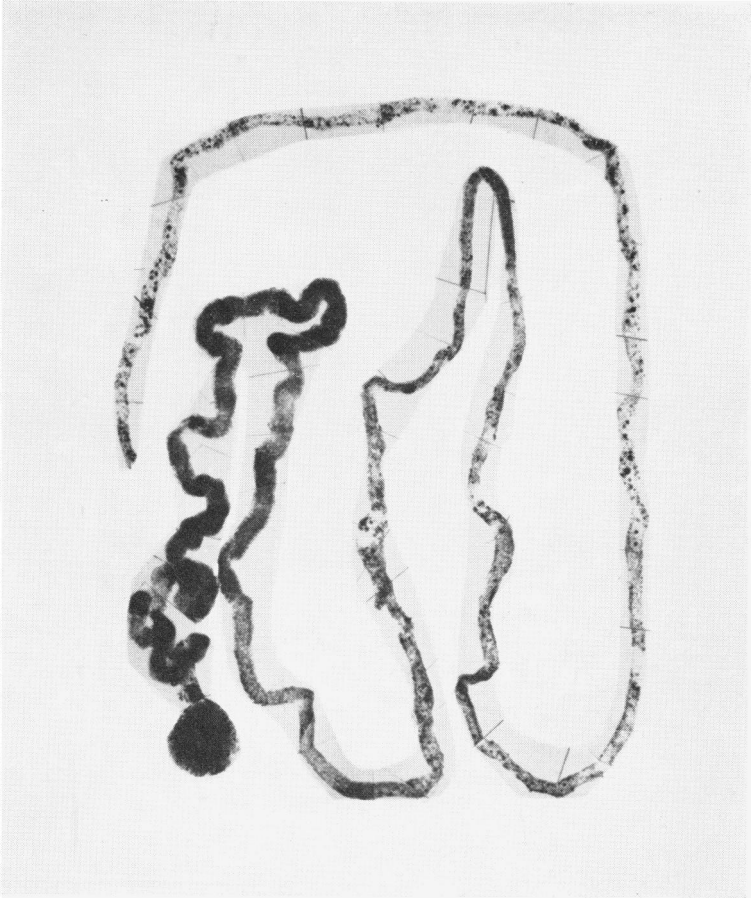

Figure 12

the "glucose threshold".

Since this is the first of the structural-functional equivalents that I shall propose, it is perhaps worthy of a short digression, particularly as it leads to a possible solution of a minor problem of correlation that arises at times in the Clinico-pathological Conference. It would seem from its structural definition, as Dr. Smith concludes from functional reasons[4, p. 38], that the glucose threshold cannot be identified with any fixed plasma concentration, since it depends on the activity of one half of tubular segments of varying dimensions. In theory, this threshold could be passed in two different ways, either by increasing the filtered load of glucose, as in diabetes, or by decreasing the reabsorption of it,

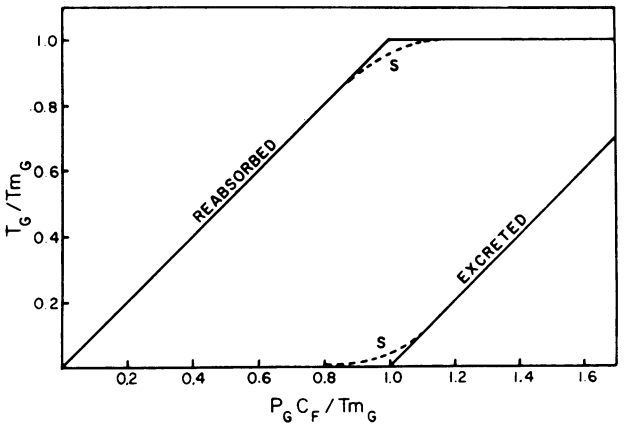

Figure 13—From Smith, H. W., *Principles of Renal Physiology*, Oxford Univ. Pr., N. Y., 1956, p. 39

as might be expected to occur with the damage to proximal convolutions that is so prominent a feature of Acute Renal Failure. As a matter of fact, the former sort of glycosuria is frequently observed clinically and the latter much less commonly; with abundant functional evidences of other forms of general tubular failure, glucose is reabsorbed even when the pathologist describes in his histological sections extensive "tubular damage". When, however, the examination is made on complete proximal convolutions with their continuity intact, as can be done only by microdissection, this paradox disappears, for a great part of the "damaged proximal", and often its physiologically most effective first portion, is found intact (Figure 12). It is therefore understandable how the "damaged nephrons" can still reabsorb a physiological load of filtered glucose with no resulting glycosuria, and also why, as will appear in more detail later, when that load is increased during the procedure of a "titration", their Tm_G is found to be reduced.

To return to the larger problem of quantitative correlation: a more detailed examination of the functional aspect of the "threshold" brings us to a critical point. If, in the presence of normal kidneys, the glucose concentration in the plasma is progressively raised, the reabsorptive mechanism is saturated, sugar appears in the urine, and after a brief period its excretion is directly proportional to the rising blood concentration; it is during the transition to this proportional glycosuria that the much discussed "splay" in the curve of excretion occurs (Figure 13).

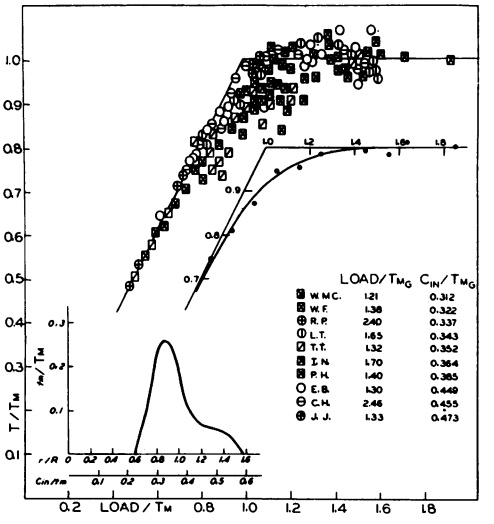

Figure 14—From Smith, H. W., *Lectures on the Kidney,* Univ. of Kansas Pr., 1943, p. 118

Two explanations have been advanced to explain its origin. It has been held that it is "overwhelmingly more likely"[20] that the splay results from a kinetic component which can be described by the Menten-Michaelis formulation of the reaction rates of the enzymatic activities responsible for the transport of glucose across the tubule wall. One theoretical analysis of this possibility has, however, found the explanation inadequate[21]. The second explanation, based on functional measurements which we shall consider later in detail, holds that the splay results from a dispersion among the nephrons of differing capabilities in filtering and reabsorbing glucose; some are quickly saturated and spill sugar early, some later, during the transition to a glycosuria proportional to the plasma level[15, p. 104 et seq.]. Why the nephrons so differ, functional evidence gives no answer, though it has been suggested that the "size" and the "shape"[22] of the structural components may be responsible. It is in answer to these speculations that our structural measurements may be helpful.

The most complete functional data for correlation are those which have been obtained by the procedure of "titration" where, on the rising concentration of plasma glucose produced by its infusion, clearances of inulin and glucose are followed past the point of tubular saturation into the range of fully established glycosuria. A detailed description of the

STRUCTURAL AND FUNCTIONAL EQUIVALENTS

Functional Measurement		*Structural Equivalent*
Rate of filtration in a particular nephron	cin	Surface of glom. tuft of a particular nephron (sq. mm.)
Glomerular filtration rate (cc/min)	Cin	Mean of all measured glom. tuft surfaces
Rate of glucose reabsorption in a particular saturated nephron (mg/min)	tm	Vol. of prox. conv. of a particular nephron (cu. mm.)
Max. value of total reabsorption in all nephrons	Tm	Mean value of all measured prox. volumes
"Glomerular Activity" (cin/tm) in a particular nephron	r	$\frac{\text{Glom. surf. (sq. mm)}}{\text{Prox. vol. (cu. mm)}}$ of a particular nephron
Total glomerular activity in both kidneys (mean value Cin/Tm)	R	Mean value of r of all measured nephrons
Relative glomerular activity of a particular category of nephrons $\frac{\text{cin/tm}}{\text{Cin/Tm}} = \frac{1}{\text{Pg Cin/Tm}}$	r/R	$\frac{\text{Glom. surf./prox. vol. of a particular nephron}}{\text{Mean value glom. surf/prox. vol. all nephrons}}$

Functional	*Definitions*	*Structural*
A group of nephrons with identical cin/tm ratios	Category of nephrons	A group of nephrons with identical glom. surf./prox. vol. ratios: determinable for particular nephrons.
Appearance of glucose in urine after saturation of all nephrons	Glucose "threshold"	Result of saturation of the reserve medullary segments of prox. conv. of all nephrons

Figure 15

procedure and a theoretical analysis of the entire physiological situation has been given by Dr. Smith and his coworkers[15, p. 104 et seq.], and I need here only call attention to certain details of definition with which we shall be particularly concerned in our correlation of its conclusions with the structural data.

In the upper curves of the graph (Figure 14) T represents the total tubular reabsorption of glucose (mg./min.) plotted against the load of filtered glucose which is calculated from the glomerular filtration rate (inulin clearance) and the plasma concentration of glucose; both are expressed as percentages of Tm, i.e., the maximum value of T. Again we see the splay of Figure 13, now inverted, at the point of inflection;

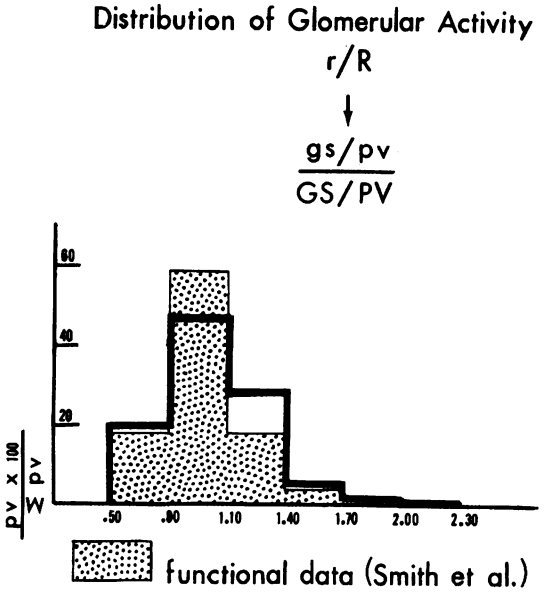

Figure 16

on the basis of the second explanation, saturation of the tubules was not coincident in all nephrons.

This dispersion in the functional capacity of the nephrons is plotted as a distribution curve in the lower half of Figure 14, in which the abscissa represents the ratio r/R with which we shall be much concerned. The value r is defined as the ratio of the inulin clearance to tm, i.e., c_{in}/tm, and has been designated by Dr. Smith[15] as "glomerular activity", since it expresses the rate of filtration (cc./min.) in the glomerulus of a particular *nephron* relative to the reabsorptive capacity in that nephron as measured by the maximal rate of glucose reabsorption in mg./min. R represents total glomerular activity of both *kidneys* and is held to be equal to the mean value of all r's. The frequency distribution curve of the ratio of r/R plotted against tm/Tm, shown in the lower part of Figure 14, is normal for the consolidated data of several human kidneys. From it the conclusion is drawn that "glomerular activity in the (human) kidney is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the observations fall within ± 40 per cent of the mean"[15, p. 117].

TABLE 1

	K W *gms.*	*No. Nephrons* *K W x 7000*	*MPV* *cu. mm.*	*Σpv* *cu. mm.*	*MGS* *sq. mm.*	*Σgs* *sq. mm.*
1038 ♂	335	2,345,000	.069	161,805	.269	630,805
1041 ♀	314	2,198,000	.077	169,246	.197	433,006
1044 ♂	268	1,876,000	.100	187,600	.327	613,452

Now it is possible to substitute in these manipulations of the functional data the corresponding structural measurements which we have previously found to have a statistically correlative relation and which we therefore believe may be most appropriate in the representation of functional activity; namely, glomerular surface area and volume of the proximal convolution. A summary of the various relations which we shall consider as structural-functional equivalents is shown in Figure 15.

Plotting the value of r/R with these structural equivalents in the same form as was used with the functional data, the frequency distributions of the two expressions, structural and functional, are found to be similar (Figure 16). The concluding statement of the functional investigators can therefore be amplified by a structural expression, namely, glomerular activity, whether derived directly from functional data or *expressed by relations of the structural dimensions of glomerular surfaces and volumes of the proximal convolution in the nephrons*, is distributed about the mean in such a manner that 95 per cent of the observations fall within ± 40 per cent of the mean.

The finding of a similar distribution of variation in the two different descriptions, structural and functional, suggests that we are dealing with phenomena that are comprised in one class, not two; but a more direct demonstration of the identity of Structure and Function in our case is possible.

We have previously mentioned the ambiguity of the concept of a "glucose threshold"; Dr. Smith has therefore proposed[4, p. 38] the ratio GFR/Tm_G as more pertinent in comparing the activity of individual kidneys; the mean value of this ratio in normal man is 0.37 ± 0.05 and in women 0.39 ± 0.06.

The structural dimensions of the three human kidneys are shown in Table 1. The calculation of the ratio by means of the structural-functional equivalents of Figure 15 is as follows:

If $\frac{Tm_G}{\Sigma pv} = C$, then $TmG = \Sigma pvC$

1038 ♂	$\frac{375}{161,805}$	0.0023		
1041 ♀	$\frac{303}{169,246}$		0.0018	
1044 ♂	$\frac{375}{187,600}$	0.0020		
		C = 0.0021	0.0018	Av. 0.0020

and if $\frac{GFR}{\Sigma gs} = C$, then $GFR = \Sigma gsC$

1038 ♂	$\frac{133}{630,805}$	0.00021		
1041 ♀	$\frac{117}{433,006}$		0.00027	
1044 ♂	$\frac{133}{613,452}$	0.00021		
		C = 0.00021	0.00027	Av. 0.00024

Dr. Smith's proposed ratio then becomes:

$$\frac{GFR}{Tm_G} = \frac{\Sigma\ gs \times \begin{matrix}0.00021\ ♂\\ 0.00027\ ♀\end{matrix}}{\Sigma\ pv \times \begin{matrix}0.0021\ ♂\\ 0.0018\ ♀\end{matrix}}$$

1038 ♂	$\frac{630,805 \times 0.00021}{161,805 \times 0.0021}$	$\frac{132.47}{339.79}$	0.38	
1041 ♀	$\frac{433,006 \times 0.00027}{169,246 \times 0.0018}$	$\frac{116.9}{304.6}$		0.38
1044 ♂	$\frac{613,452 \times 0.00021}{187,600 \times 0.0021}$	$\frac{128.82}{393.96}$	0.32	
		Av.	0.35	0.38
		Smith, observed $\frac{GFR}{Tm_G}$	0.37 ± 0.05	0.39 ± 0.06

Before our examination of the final correlation of the structural and functional measurements in the form of a complete titration curve, it is possible to test and confirm the conclusions so far drawn from measurements on human kidneys by examining the situation in the dog; here we shall have the great advantage of correlating functional and structural

CORRELATION COEFFICIENTS OF DOG NEPHRON MEASUREMENTS

	Y Glom. Surf. sq. mm.		U Glom. Vol. cu. mm.		X Prox. Length mm.		Z Prox. Volume cu. mm.	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Cora N = 47	.1498	± .0155	.0055	± .0011	20.98	± 1.75	.0713	± .0080
Eleana N = 45	.1228	± .0237	.0041	± .0013	22.02	± 2.36	.0630	± .0141

	Cora D.F. 45	Eleana D.F. 43
Glom. surf/prox. vol.	rYZ .6197*	rYZ .2936**
Glom. vol/prox. vol.	rUZ .4937	rUZ .2679
Glom. surf/prox. length	rYX .2778	rYX .1701
Glom. vol/prox. length	rUX .2122	rUX .1889

*Highly significant 0.1% **Probably significant 5.0%

Figure 17

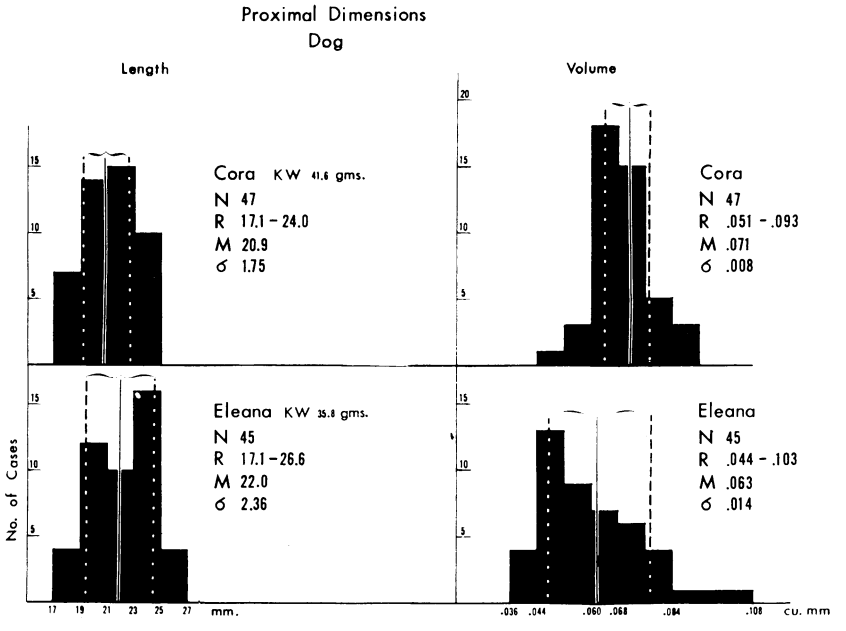

Figure 18

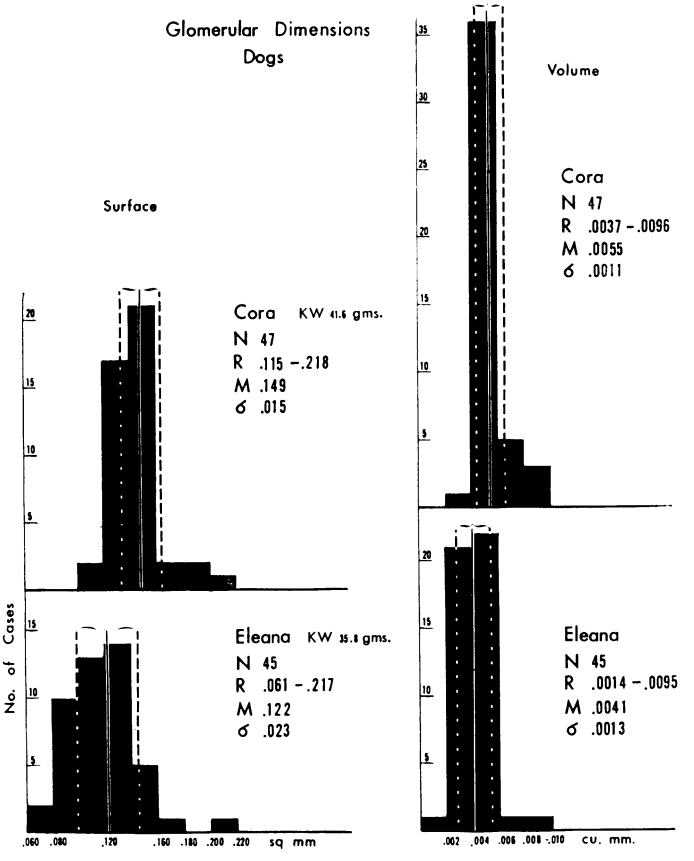

Figure 19

measurements made on the same kidney and on kidneys which vary in size. Moreover, we shall be examining an organ which is supposed to differ somewhat from that of man in that when functionally examined it appears to be more homogeneous in the population of its nephrons; as a result, the splay in the curve of glucose titration in the dog has been found to be less pronounced.

A different form of statistical evidence, confirming our previous conclusion that glomerular surface and proximal convolution volume are the proper structural measurements to use in comparison with the functional data, is seen in the calculated coefficients of correlation in two animals (Figure 17). It is at once apparent that the kidneys of dogs may vary as much as do those of men. In the more "regular" dog (Cora) the highly significant figure for the relation of glomerular surface-

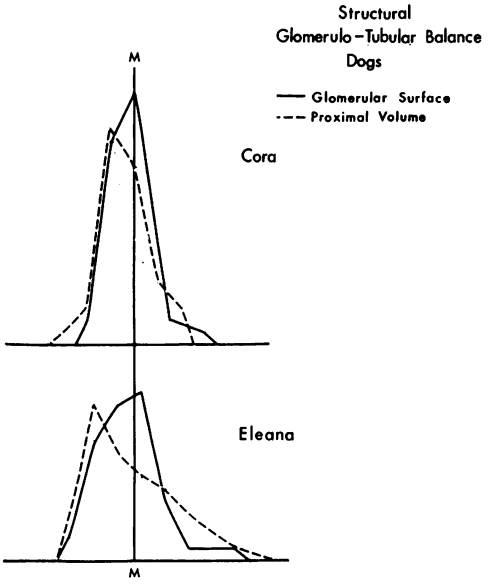

Figure 20

proximal volume is apparent; in the "irregular" kidney of the other (Eleana) the coefficient is much less significant, but it is more so for glomerular surface-proximal volume than for any comparison between the other glomerular and tubular dimensions of this animal.

The first conclusion to be drawn from an examination of histograms representing the structural dimensions (Figures 18, 19) is that the kidneys of normal dogs vary more markedly in their structural components than has been suspected from previously recorded functional examinations; indeed, one animal (Cora) shows a more homogeneous population of nephrons than is usually seen in humans; in the other (Eleana) the spread of frequency distribution is greater; moreover, the distribution of proximal convolution volume shows a decided skew. Even with these bare structural data and without recourse to the calculation of ratios, a superimposition of the means of the histograms of glomerular and proximal dimensions, now transformed into polygons, allows us to visualize, as it were, and to see how and even why tubulo-glomerular balance differs in the two dogs (Figure 20). The two curves representing glomerular and tubular dimensions of the "regular" kidney of Cora lie closely contiguous, whereas those from Eleana are separate and form two definite peaks, while the slight skew in the tubular dimen-

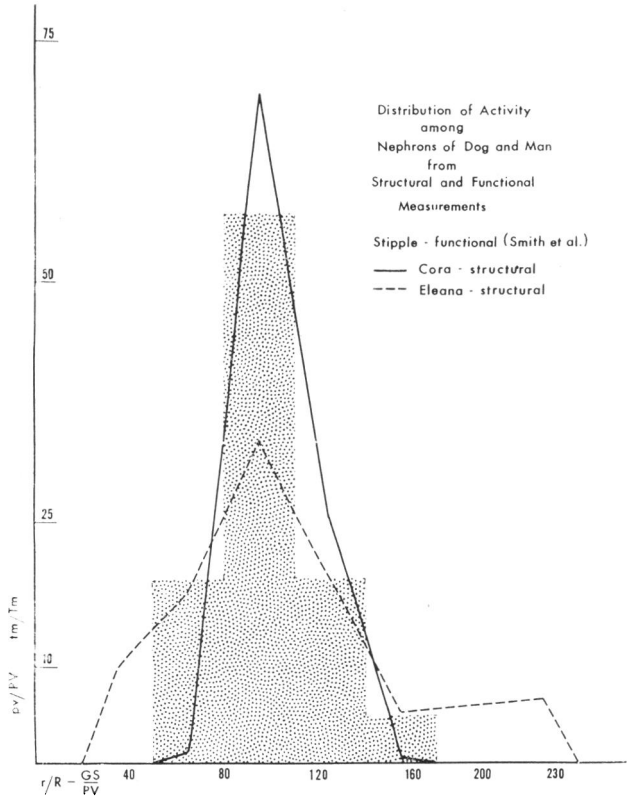

Figure 21

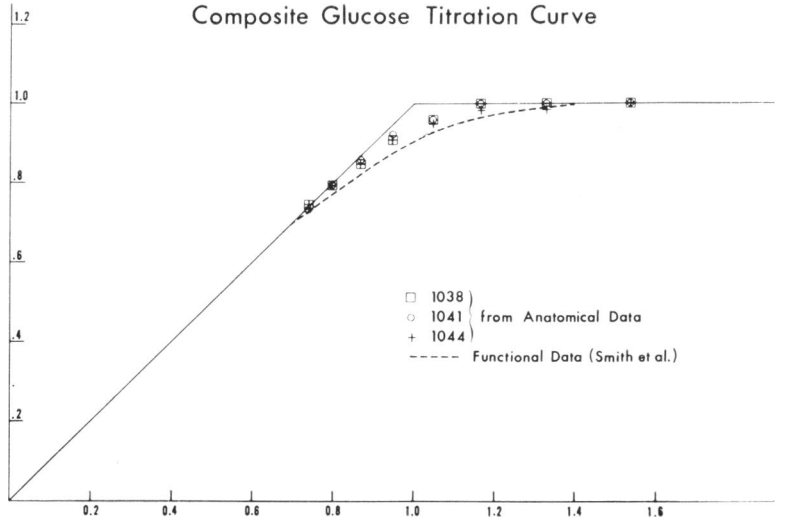

Figure 22

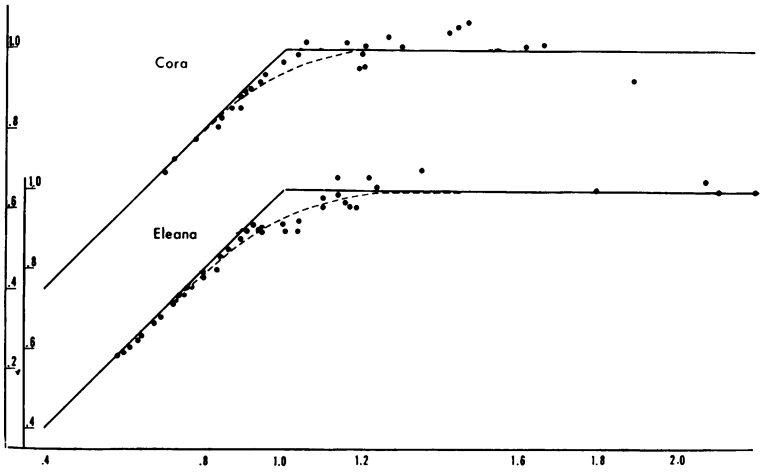

Figure 23

sions of the former is greatly exaggerated in the latter. In the light of these differences we may therefore anticipate an interesting and perhaps crucial test when we attempt our definitive correlation with function in the two animals.

Proceeding now to a comparison of the distribution of glomerular activity in the nephrons of the two dogs, the ratio r/R against tm/Tm can be calculated in the same way as was used with the structural-functional equivalents of the human kidney; when the results are compared (Figure 21) it is clear that in the case of the "regular" dog (Cora) the polygon of the frequency distribution of "glomerular activity" as it is expressed from structural data shows a closer cluster about the mean than is observed in the human kidney, the distribution of which is shown by the superimposed stippled histogram. In the case of the other dog (Eleana), however, a much wider spread is observed than is typical for man.

Various other correlative expressions might be given using the data obtained by the structural measurements in the dogs but let us now turn to the consideration of the definitive functional expression in man and the two animals as it is expressed in the conventional glucose titration curve (Figures 22, 23).

As a matter of fact, what is presented in the two figures can hardly be called "conventional" curves, for a certain artfulness has entered into their preparation. Perhaps the term "composite" would better de-

scribe them, for in the case of the human kidney (Figure 22) the dotted line with its splay is taken from Dr. Smith's previous Figure 14, where it was drawn by visual approximation to fit the points of the actual functional determinations. The points in Figure 22, however, were calculated by means of structural-functional equivalents from the anatomical dimensions; as is evident, they approximate the functional line well within the bounds of expected variability and error.

In the case of the dogs (Figure 23) I have deliberately confused matters in order to emphasize the equivalence of the functional and structural measurements; the points of the figure are the actual functional determinations of Dr. Bradley's group, whereas the dotted line is calculated from the anatomical dimensions. As can be seen, the splay in the "regular" kidneys of Cora is less than that of the human cases and fits the functional points as well as would the visual approximation of a smoothed curve. In the more "irregular" kidneys of Eleana, the splay is greater.

We thus have come to an identical quantitative description in gm.-cm.-sec. units of the handling of glucose by the nephrons and kidney by measuring either the dimensions of their Structure or the magnitude of their Function. Specifically, Tm_G, GFR and their ratio, Tm_G/GFR can be derived from either the structural components or from the movements of glucose between blood and urine; or the two sorts of measurements can be combined in an expression, the titration curve with its splay, that describes the course of the process. How, then, are we to define "the nephron" in terms that will include the unity of its structural and functional aspects?

If we depart from the assumption of a duality of its Structure as opposed to its Function, we arrive in our final mathematical expressions at an identity. Two descriptions, one of a curiously contrived physical lump and another of a "Dynamic" that in some undefinable manner informs its substance, seem not only superfluous but otiose, for to return to the analogy of Professor Ryle, the clock and its ghostly inhabitant prove to have the same dimensions and therefore presumably the same extension in space and time. Our ghost, thus taking on the attributes of the body which contains it, loses its spectral identity and the illusion of the duality that created it vanishes.

As to what remains, we must return to our earlier description of the nephron as a manifestation of phenomena occurring on a series of infinitely regressing levels of organization[13]. To the present the biologists can follow this descent into the infinite only a certain distance; in its structural aspect, the morphologist approaches with electron microscopy to the molecular level, while in its "dynamic" functional aspects, the physiologist and biochemist do somewhat better in their measurement of the movements of ions; beyond these, we must draw on the revelations of the physicists for comprehension of what we cannot as yet see and measure.

How then can the morphologist better describe the nephron than in the words of the poet of two thousand years ago, where the "atoms" within the luminal fluid in their ceaseless and varied motions ("magis adsiduo varioque exercito motu". De Rerum Nat. II, 100) "swerve" in ordered procession to give the appearance of dynamic functional activity as they pass through tubule cells which are themselves collocations of the same atoms arrested ("et quaecumque magis condenso conciliatu". De Rerum Nat. II, 100), but only for the moment, in the ever-renewing patterns of denser aggregations which we know as structural Form? And if this description leaves him with an uncomfortable feeling, as it apparently did Aristotle, who complained of the "laziness" of the Epicureans in their neglect of a more detailed analysis of the "motions" of their atoms, and he still senses a duality between the "billiard balls" and their "movement", he may, leaping 20 centuries in time, follow the philosopher Russell in his transformation of the Democritean "particle" into the Einsteinian "particle-event"; and with "events" all that remains is that something is observed to occur in a space-time relation the description of which depends on the position of the observer[23, p. 832].

If the speculative Morphologist thus moves with what may seem a suspect facility on atomic levels of conceptual abstraction, the skeptic, or should I say the practical man, will probably listen to a certain point, but eventually comes the Johnsonian reaction. For his common sense refuses to believe that the stone in the path before him is not indeed the inert clod which the worthy Doctor kicked so violently in his refutation of the Bishop's fancy that things are not what they seem to be. Had he been aware that, in the aspect of its dynamic activity, the stone was rather like a swarm of bees in its atomic configuration, the demonstration might have seemed to him not only futile but even hazardous.

But in our case it was at just such a concrete and common sense level as the stone in the path, the nephron with its glomerulus and convolution, that the duality of Structure and Function was found illusory. The testimony of the physicists and philosophers need only be accepted to encourage the morphologist to carry the analysis into realms of organization not yet open to his methods.

In a more comprehensive definition, the nephron thus becomes a locus of certain defined biological activities, a process* of "events," to use Russell's terms, which can be described from the two different viewpoints which it is convenient to call its structural and its functional aspects.

It was not in the observed, but in the observer that our refuted duality lay. And the Pathologist turns again to the physicist for illustration and quotes as once before, at a time when demonstration still eluded him[24], Schroedinger's analogy in the resolution of his similar problem, where, as he says, "in the same way Gaurisankar and Everest turn out to be the same peak seen from different valleys"[25]. Successful correlation, in compliance with the final clause of our definition of the "nephron", thus becomes a maneuver of the observer into the fortunate position where what appears to be two is seen to be one.

Now it is immediately apparent that the finding of such observation posts will not be a simple matter when one considers the series of infinite regress in levels of structural organization that I have previously described, where from "kidney" to intracellular "microsomes" we continue on, our imagination sparked by the physicists, through molecules and atoms, electrons and lesser "particles" and ultimately to the philosopher's "event". The point of correlation may lie on any step of this descent; where shall the observer pause for his comprehensive view of the unity which he seeks?

A clue towards the answer can perhaps be found in the fact that the procedure of quantitative correlation contains within itself a guiding principle for its resolution. For our basic assumption, long supported by observational verification of past experience, is that in the biological process the very origin, development and definitive growth and form of the structural components *are* functional, i.e., adaptive, adjustments to environmental change and that, as a sort of "steady state", the whole phenomenal complex is so intimately tied together as to be indivisible.

*I use the word "process" since the nephron is manifested as a multitude of events which leads to the transformation of blood into urine.

A statistical examination of the various structural data of the problem may therefore reveal some particular and pertinent relation and so mark the point of correlation.

We were fortunate in our case that the correlation point lay on a readily accessible level and that we needed to assume but four possible correlates, surface and volume of the two structural components of the process. If difficulties and complications are to be anticipated when the investigator is involved in his quantitative measurements on the level of intra-mitochondrial membranes and the movements of molecules and ions under enzymatic control, surely in these days of ever-increasing technical facility, we cannot deny its eventual accomplishment.

Having thus ejected Duality through the front door on the easily accessible level of structural-functional organization and circumspectly barred its reentrance through the subterranean corridors where the activity of the enzymologists and seekers after "fine Structure" so busily reverberate, I am aware of the host of more immediately practical questions that may be raised regarding the general applicability of what may seem an over-simplified resolution of the problem of correlation.

From what has been said it follows that successful quantitative correlation of the structural and functional aspects of any renal activity is strictly dependent on certain requirements.

First, the functional data must be based on an accurate description and localization of the activity in the nephron and on equally certain and measurable structural characteristics. The direct methods of micropuncture and microdissection have fulfilled these requirements in the case of the handling of glucose; I am not aware of any other example of renal activity for which the data have been thus firmly established.

Secondly, the measurements, structural and functional, must be made under defined standard conditions which can be regarded as representing a base line of normality if for no other reason than that the normal situation presents in the relation of its structural and functional aspects a "steady-state" which is determinable. For the abnormal situation, the difficulties of definitively measuring a "drifting" potential across a damaged membrane might be considered analogous.

These requirements would seem to preclude for the present the application of the correlative procedure to a situation where observation shows a departure from the structural relations known to be usual (normal) for undisturbed physiological activity. The effects of any

such departures cannot be predicted from the simple datum of their morphological appearances. To take perhaps the simplest case: a "thickened glomerular membrane", even if its thickness be quantitatively expressed, may be not less permeable but more so, for such is true of a freshly prepared, thick collodion membrane as compared to a thin, dried preparation. And the complexity of the possible effects of tubular cell changes staggers even the imagination.

In the *normal kidney* both the structural and functional characteristics of the *nephrons* have been directly measured[19], and it is *only* on the basis of these data and the relative homogeneity of its constituent units, that the analysis[15, p. 104 et seq.] of the situation in the *kidney* is possible by means of the over-all datum of the glucose clearance. The structural and functional measurements are found under these conditions to be equatable.

In the *abnormal kidney*, the structural *heterogeneity* of the abnormal nephrons is obviously apparent[3, 26] but direct measurement of this heterogeneity is impossible, since the variability is not only infinite, both qualitatively and quantitatively, but is involved in the infinite regress of alterations in the nephron, convolution, cell, mitochondrion .... The *functional* characteristics of the structurally altered individual nephrons are entirely unknown, and attempts at their determination by direct examination would be subject to the same difficulties as is the case for the structural measurements.

It would therefore seem hazardous, in the abnormal situation where the only information available concerning the structural changes is that they exist and there is none at all concerning the functional characteristics of the altered units, to attempt an analysis of the *abnormal kidney*, which is the sum of these unknowns, from the datum of a "clearance", the interpretation of which is furthermore prejudiced by demonstrable[27] alterations in its functional significance*.

*Yet it has been suggested, since the glucose clearance failed to indicate a qualitative difference (degree of splay) between various sorts of experimentally abnormal kidneys, that, whatever (undescribed) structural alterations may have been present in the nephrons, these did not affect the functional product other than to decrease its totality; the "bizarre" nephrons, it is concluded, functioned either normally or not at all[28]. This hypothesis is then extended by closely reasoned clinical argument to include all the various forms of chronic renal failure that occur in man. To the morphologist, this denial of functional significance to the multiplicity of structural alterations that are so evident to him, seems a renaissance of the Great Negation which he previously considered (p. 87) and therefore he sees no need to accept more than the negative factual findings of the experiment and to conclude again[27] that in the description and analysis of the abnormal kidney, the clearance is a poor instrument and has failed. How such a failure might come about is implicit in a subsidiary footnote of the article in question[28, p. 92]. It might be added that the use of the term "autoregulation", which seems to suggest a complexity which would make this alternative to the "Intact Nephron Hypothesis" of the text unlikely, could in the case of the glucose Tm be accomplished by a combination of the simple compensating structural changes of "atrophy" and "hypertrophy", either glomerular or tubular, and these are ever-present structural alterations in any chronic renal lesion.

In the case of the functional data, certain departures from the basic conditions of "normality" disturb the quantitative identity of the correlation in a somewhat more comprehensible manner. Cooling the kidneys lowers the Tm_G by two thirds with, it may be safely assumed, no such proportionate decrease in the volume of the proximal convolutions[29]. It would seem certain that this disturbing effect has operated on the structural-functional level of the energy-transforming system rather than on the grosser structural components; the analogy of the loss of efficiency in a steam engine with dampened fires but intact in its structural members might be appropriate; and at the level of energy transformations, as we have seen in our definition of the nephron as a series of events, it is meaningless to distinguish between Structure and Function*.

The action of phlorizin, which would completely destroy the quantitative correlation of Tm_G and Σpv observed in the normal kidney, is of especial interest as illustrating a disturbance which apparently occurs at a level of structural-functional organization remote from that which is concerned in the correlation under physiological conditions. Recent work indicates that phlorizin produces mitochondrial alterations and the evidence is "in some ways consistent with membrane theory"[30]. If any correlation were to be sought, it would seem that the data must be derived from the appropriate structural-functional level of mitochondrion and intracellular membrane.

In the face of these complexities that confront the Morphologist as he looks towards the extension of the procedures of structural-functional correlation to wider areas of renal activity, an attitude of optimistic Hope seems warranted. He admits both his factual ignorance and his technical limitations, and it is in them that he finds the reasons for anticipation of future difficulties and possible failures, rather than in metaphysical doubts as to the validity of his premises; for in the one case, where technical facility afforded the opportunity for exact quan-

*The conclusion that the antithesis of Structure and Function is meaningless affords an example of the operation of the methods of Linguistic Analytics and Logical Positivism in the clarification of at least certain metaphysical dilemmas. If one postulates *a priori* the duality, "Structure-Function", and then asks the classic question as to which is "cause" and which "effect", the answer is not that in one situation "Structure has determined Function" and in another that "Function has determined Structure" as, for example, is presumed by the analogy of Childs which we cited. A little reflection will show that in *any* specific case the argument may run in either direction; the only possible solution would be to toss the two labels in a hat and whichever were drawn would be the "right" answer. Citing the absurdity of this method of deciding between Cause and Effect might have appealed to David Hume in his elimination of the common-sense element of necessity which before his time informed the causal relation, as it illustrates that, at best, "cause" and "effect" are a description of a temporal sequence.

But if we are dealing with the *structural* and *functional* aspects of *one* thing, renal activity, the meaningless question as to whether it is "causing" itself does not arise.

titative measurement, Structure and Function were found identical in their dimensions. And in the recognition of the organ as a regressing and converging series of structural-functional levels of organization, the Duality that has "harassed . . . biological thought . . . throughout its history"[11, p. 326] vanishes in the realm of the infinitely small, where distinctions, other than that of observed events, are lost and only the "atoms and their eternal motions" remain—*sponte sua volitent aeterno percita motu* (De Rerum Nat. III, 33).

It comes as a humbling and perhaps a well-timed admonition in these days of over-proud technical achievement that at this point in the evening's entertainment, each will turn to his neighbor and say, "Is this not where we came in—2,000 years ago?"* For "in this molecular-atomic world Function seems not so much to rest on Structure" as that each is of the other's essence.

Such at least is the Faith of the Morphologist, founded, as the most eminent of authority both secular[2, p. 314] and clerical[31] commands, on the evidence of things *as yet* unseen. And if thus, with the admission of Hope and Faith (Charity surely having been implicit throughout), the Morphologist seems to stray from the narrow path of an absolute and intransigent Scientism, he now walks with his humanistic brothers supported by these most necessary of human adjuncts: he will not therefore easily be discouraged.

*In a conversation between Swinburne and Matthew Arnold, the former is reported to have boasted that the poet by pure intuition had thus anticipated by twenty centuries the scientists who depend on reason alone. Apart from this Victorian attitude, which made the scientist a dull fellow with no spark of poetic fancy (and what better example to the contrary can be cited than the imaginative arabesques which decorate renal theory), Swinburne was apparently unaware that the atomic constitution of matter had been empirically "established" by the early Atomists, who, grinding friable substance in a mortar, were never able to grind it away. With their technical facilities they could do no more; the physicists of today use the same experimental method (the disintegration of matter) and after the expenditure of infinitely greater forces, the "particles" remain. There is therefore no antithesis (the last I shall mention) between the vision of the poet and that of the scientist.

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